UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/820,099	03/27/2001	Jan G.J. van de Winkel	MXI-170RCE	2545

59819 7590 02/05/2008
LAHIVE & COCKFIELD, LLP/MEDAREX
ONE POST OFFICE SQUARE
BOSTON, MA 02109-2127

EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
02/05/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/820,099	VAN DE WINKEL, JAN G.J.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-12 and 35-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 6-12 and 35-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 31 October 2007 has been entered.

2. Claims 2-5 and 13-34 are canceled.

Claims 35-41 have been added.

3. Claims 1, 6-12 and 35-41 are pending and under consideration.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. This Office Action contains New Grounds of Rejections.

Rejections Maintained

6. The rejection of claims 1 and 6-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as introducing new matter is maintained. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The response filed 10/31/2007 states that contrary to the examiners assertion, it is clear from the specification that the invention is based on the discovery that monomeric (serum) IgA binds to FcαR-expressing cells and causes elimination (e.g., phagocytosis) of antigens or target cells bound to monomeric IgA (citing summary of invention at pg. 2, lines 20-26). Applicant states that the very focus of the present application is to harness this feature of monomeric IgA to eliminate a target cell (i.e., a cancer cell) or antigen (i.e., bacteria, virus or fungus) from the circulatory system of a

subject. Applicant points to at least pg. 2, line 20 through pg. 3, line 32; pg. 12 (lines 33-35); pg. 13 (lines 1-21); pg. 14 (lines 19-33) and in original claims 1-3 and 7-8. Applicant concludes that it is clear that monomeric IgA for treating cancer and infections is clearly and explicitly contemplated within the four corners of the present specification, and is the central aspect of the invention. Applicants' arguments have been fully considered but are not found persuasive. As stated in the previous Office Action, the examiner agrees that Applicants' invention is based on the discovery that monomeric IgA-antigen complexes are efficiently phagocytosed by FcαR-expressing cells (i.e., Kupffer cells), whereas secretory (dimeric) IgA does not initiate phagocytosis, however, the claimed method recites that a subject is administered a composition comprising monomeric IgA that binds to FcαRI and an agent which specifically binds to the target cell (e.g., cancer cell) or antigen (e.g., bacterial, viral or fungal antigen), wherein the agent is an antibody or an antigen-binding fragment thereof. Thus, in contrast to applicants' arguments the claimed invention is based on "an agent" which is an antibody or antigen-binding fragment thereof and not necessarily monomeric IgA. The claims do not require that monomeric IgA bind the antigen such that the antigen or target cell is eliminated by phagocytosis as argued and disclosed in the present application. The as filed disclosure, including the pages and claims cited by Applicant do not disclose a composition comprising monomeric IgA and a separate "agent", which is an antibody or antigen-binding fragment thereof that binds the target cell or antigen, wherein administration of the composition to a subject eliminates the target cell or antigen from the circulatory system of the subject. Since, it is the "agent" (antibody or antigen-binding fragment thereof) that binds the target cell or antigen, where is it disclosed in the as filed specification or claims that the "agent" (antibody or antigen-binding fragment thereof), other than monomeric IgA, binds the target cell or antigen and causes phagocytosis of the target cell or antigen? The as filed specification discloses that it is the Fc region of monomeric IgA that interacts with FcαRI expressed on liver Kupffer cells and causes elimination (e.g., phagocytosis) of monomeric IgA-antigen complexes. The specification does not disclose the elimination of "an agent" which is an antibody or

antibody fragment thereof which is claimed to specifically bind the target cell or antigen, not monomeric IgA. Again, as noted by the examiner in the previous Office Actions, the specification as filed appears to provide adequate written description for (i) the administration of serum IgA (monomeric), *but not linked by chemical conjugation or recombinant genetic fusion* to an agent or antibody that binds a target cell or antigen and causes the elimination of said target cell or antigen and (ii) bispecific antibodies that bind "outside the natural ligand binding domain of the trigger receptor" (specification at pg. 9, lines 19-20) to circumvent interference by serum antibodies, wherein the linkage of the two binding components (i.e., Fab) of the bispecific antibody are linked by chemical conjugation or recombinant genetic fusion. The as filed specification as pointed to by Applicant does not provide adequate written support for a method of treating cancer, or treating bacterial, viral and fungal infections comprising administering monomeric IgA and an antibody or antibody fragment thereof (i.e., agent) which specifically binds to the target cell, i.e., cancer cell or a bacterial, viral or fungal antigen. The as filed disclosure as pointed to by applicant does not disclose a composition comprising monomeric IgA and an antibody or antigen-binding fragment thereof (e.g., an "agent") that binds a cancer cell or a bacterial, viral or fungal antigen for the elimination of the cancer cell, or bacterial, viral or fungal infection.

As currently presented, the claims recite limitations, which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C 112. Applicant is required to provide sufficient written support for the limitations recited in the present claims in the specification or claims, as filed, or remove these limitations from the claims in response to this Office Action.

7. The rejection of claims 1 and 6-12 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of eliminating a target cell or

antigen from the circulatory system of a subject comprising administering monomeric (serum) IgA or administering a bispecific antibody comprising an antibody fragment that binds FcαRI outside the natural ligand binding domain and an antibody fragment that binds a target cell or antigen, wherein the antibody fragments of the bispecific antibody are linked via chemical conjugation or by recombinant genetic fusion, does not reasonably provide enablement for a method of eliminating a target cell or antigen from the circulatory system of a subject comprising administering monomeric IgA and an agent/antibody/antibody fragment that binds a target cell or antigen as embraced by the claims is maintained.

The response filed 10/31/2007 states that applicants' have enabled a method of eliminating a target cell or antigen from the circulatory system of a subject by administering monomeric IgA and an agent (e.g., an antibody or fragment thereof) that binds a target cell or antigen. Applicant refers to their above remarks, in which Applicants' teach that monomeric (serum) IgA binds to FcαR-expressing cells and causes elimination (e.g., phagocytosis) of antigen or target cells bound to monomeric IgA. Applicant reiterates that the focus of the present application is to harness this feature of monomeric IgA to eliminate a target cell. Applicant refers to pg. 2, line 20 through pg. 3, line 32; pg. 12 (lines 33-35); pg. 13 (lines 1-21); pg. 14 (lines 19-33) and in original claims 1-3 and 7-8 as sufficiently enabling the claimed invention. Applicants' arguments have been fully considered but are not found persuasive. Applicant continues to argue that the claimed invention is based on the finding that monomeric (serum) IgA binds to FcαR-expressing cells and causes elimination (e.g., phagocytosis) of antigen or target cells bound to monomeric IgA, however, the claims specifically recite that it is the agent, not monomeric IgA that binds the target cell or antigen. Thus, applicant's arguments are not commensurate in scope with the claims. The claims remain drawn to a method of eliminating a target cell or antigen from the circulatory system of a subject comprising administering monomeric IgA and an agent that binds a target cell or antigen wherein the agent is an antibody or antibody fragment thereof and the target cell is a cancer cell or the antigen is a bacterial, viral or fungal antigen. Thus,

the claims encompass the administration of monomeric IgA and any "agent", or just any antibody or antibody fragment that binds a target cell or antigen for the elimination of the target cell or antigen, whereas as noted by applicant the focus of the disclosure relies upon monomeric IgA binding to FcαR-expressing cells which causes elimination (e.g., phagocytosis) of the target cell or antigen.

It is reiterated that the specification teaches that the administration of serum IgA (monomeric) complexed with antigen as causing the elimination of antigens bound to monomeric IgA and (b) bispecific antibodies that bind "outside the natural ligand binding domain of the trigger receptor" (specification at pg. 9, lines 19-20) to circumvent interference by serum antibodies, wherein the two binding components (i.e., Fab) of the bispecific antibody are linked by chemical conjugation or recombinant genetic fusion. The specification also teaches that tumor specific mAb of human IgA class are not available and serum IgA may interfere with the activity of IgA mAbs under physiological conditions (pg. 9). The specification teaches that dimeric IgA (SIgA) was unable to initiate phagocytosis (see pg. 8). The specification does not teach a method of eliminating a target cell or antigen, inclusive to a cancer cell, a bacterial, viral or fungal antigen comprising administering monomeric IgA that binds to FcαRI and an agent or antibody that binds said target cell or antigen. There are no working examples of a method of eliminating a target cell or antigen, inclusive to a cancer cell, a bacterial, viral or fungal antigen comprising administering monomeric IgA that binds to FcαRI and an agent or antibody that binds said target cell or antigen. Thus, the scope of the claims is broad relative the enablement of the present application. The scope of the claims must bear a reasonable correlation with the scope of enablement. See *In re Fisher*, 166 USPQ 19 24 (CCPA 1970).

The is insufficient evidence or nexus between the administration of just any antibody or antibody fragment thereof that binds a target cell or antigen and mediates the elimination of the target cell or antigen by initiating FcαRI-mediated phagocytosis, since it is monomeric IgA which binds FcαRI thereby initiating FcαRI-mediated phagocytosis. For example, Deo et al (The Journal of immunology, 160:1677-1686,

1998, IDS reference field 1/22/2002) teach that a single class of IgA FcR binds to monomeric IgA, known as FcαRI or CD89. FcαRI binds both antigen-complexed and monomeric IgA1 and IgA2, and cross-linking of FcαRI on myeloid effector cells by polymeric IgA, IgA immune complexes, or mAbs specific for epitopes within or outside the ligand-binding domain stimulates degranulation, superoxide release, secretion of inflammatory cytokines, endocytosis and phagocytosis. There is insufficient guidance and direction to assist those skilled in the art in practicing the claimed invention comprising administering monomeric IgA and an antibody or antibody fragment thereof (i.e., an "agent") that binds a target cell or antigen for eliminating a target cell or antigen from the circulatory system of a subject. Applicant has not taught the genus of agents, antibodies or antigen-binding fragments thereof that bind the target cell or antigen, other than monomeric IgA, which bind to FcαRI thereby initiating FcαRI-mediated phagocytosis and hence, elimination of the target cell or antigen from the circulatory system of the subject.

In view of the lack of the predictability of the art to which the invention pertains as evidenced by Deo et al, the lack of guidance and direction provided by applicant, and lack of working examples of a composition comprising monomeric IgA and an antibody or antibody fragment thereof (i.e., an "agent") that binds a target cell or antigen for eliminating the target cell or antigen from the circulatory system of a subject, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods, commensurate in scope with the claimed invention.

New Grounds of Rejections

8. Claims 35-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter, which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The response filed 10/31/2007 has introduced NEW MATTER into the claims. Newly added claims 35 and 36 recite a method for eliminating a cancer cell from the circulatory system of a subject comprising administering to the subject a composition comprising monomeric IgA. The response points to pg. 3, lines 26-32 and pg. 14, lines 19-25 and original claim 7. This has been fully considered but is not found persuasive. The as filed disclosure at pg. 3 and pg. 14 disclose the elimination of cancerous liver cells by targeting cytotoxic agents, particularly a chemotherapeutic agent to FcαR-expressed on the liver cells using monomeric IgA. Originally filed claim 7 recites a method for eliminating a cancer cell from the circulatory system of a subject comprising administering a complex comprising a first portion that specifically binds FcαR-expressed on liver Kupffer cells, or which specifically binds monomeric IgA or the Fc region thereof, linked to a second portion which specifically binds a cancer cell. The as filed disclosure of monomeric IgA for targeting a cytotoxic agent to cancerous liver cells and a complex comprising a first portion that binds monomeric IgA (but is not monomeric IgA) linked to a second portion that binds a cancer cell, does not provide adequate written support for the claimed method of eliminating cancerous cells in a subject comprising administering monomeric IgA because the disclosure as pointed to would not have reasonably led the skilled artisan to the claimed method of administering monomeric IgA for the elimination of cancerous cells. Further, the specification discloses that "Tumor specific mAb of human IgA class are not available" (pg. 9, line 7). The disclosure that tumor specific human IgA monoclonal antibodies are not available would not have led one skilled in the art to a method for eliminating a cancer cell from the circulatory system of a subject comprising administering to the subject a composition comprising monomeric IgA.

Newly added claims 35-36 now recites limitations, which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in newly added claims 35-36, which did not

appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C 112. Applicant is required to provide sufficient written support for the limitations recited in newly added claims 35-36 in the specification or claims, as filed, or remove these limitations from the claims in response to this Office Action.

9. Claims 35, 37 and 40-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Mannhalter et al (U.S. Patent 5,808,000, issued 9/15/1998, cited on PTO-892 mailed 1/26/2006).

The claims are drawn to a method for eliminating a target cell or antigen from the circulatory system of a subject comprising administering to the subject a composition comprising monomeric IgA wherein the target antigen is selected from a bacteria, a virus and a fungus and wherein the composition is administered by injection or intravenously.

Mannhalter et al teach a method of treating inflammations, infections and allergies, including bacterial and viral infections in a subject comprising administering monomeric IgA by intravenous injection (see entire document, particularly columns 6-7 and 1).

Thus, Mannhalter et al anticipate the claims.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 35 and 37-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mannhalter et al (U.S. Patent 5,808,000, issued 9/15/1998, cited on PTO-892 mailed 1/26/2006) in view of Deo et al (The Journal of immunology, 160:1677-1686, 1998, IDS reference filed 1/22/2002).

Claims 35, 37 and 40-41 have been described supra.

Claims 38-39 recite that the method further comprises the administration of a cytokine which increases expression of FcαRI on Kupffer cells, wherein the cytokine is GM-CSF, IL-6, IL-1β, Il-8 and TNF-α.

Mannhalter et al have been described supra. Mannhalter et al do not specifically teach administration of a cytokine selected from GM-CSF, IL-6, IL-1β, Il-8 and TNF-α. This deficiency is made up for in the teachings of Deo et al.

Deo et al teach that only FcαRI binds monomeric IgA, wherein FcαRI expression can be enhanced by TNF-α or GM-CSF and IgA immune complexes or monoclonal antibodies specific for epitopes within or outside the FcαRI ligand-binding domain

stimulates degranulation, superoxide release, secretion of inflammatory cytokines, endocytosis and phagocytosis (see entire document, particularly pp. 1677).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method of treating inflammations, infections and allergies, including bacterial and viral infections in a subject comprising administering monomeric IgA and GM-CSF or TNF-α.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method of treating inflammations, infections and allergies, including bacterial and viral infections in a subject comprising administering monomeric IgA and GM-CSF or TNF-α in view of Mannhalter et al and Deo et al because Mannhalter et al teach a method of treating inflammations, infections and allergies, including bacterial and viral infections in a subject comprising administering monomeric IgA and Deo et al teach that only FcαRI binds monomeric IgA, wherein FcαRI expression can be enhanced by TNF-α or GM-CSF and IgA immune complexes or monoclonal antibodies specific for epitopes within or outside the FcαRI ligand-binding domain stimulates degranulation, superoxide release, secretion of inflammatory cytokines, endocytosis and phagocytosis. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to combine TNF-α or GM-CSF with monomeric IgA with the goal of increasing FcαRI-mediated activity (e.g., phagocytosis) in patients suffering from bacterial or viral infections. Thus, it would have been *prima facie* obvious to one skilled in the art to have produced a method of treating inflammations, infections and allergies, including bacterial and viral infections in a subject comprising administering monomeric IgA and GM-CSF or TNF-α in view of Mannhalter et al and Deo et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Rifai et al. J. Exp. Med. 160:125-137, July 1984. Rifai et al teach that removal of soluble immune complexes of dimeric IgA and monomeric IgA from circulation is mediated by a specific IgA receptor on Kupffer cells.

13. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Blanchard/
Primary Examiner, A.U. 1643